ATENT COOPERATION TRE Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 13 June 2000 (13.06.00)	
International application No. PCT/EP99/07768	**Applicant's or agent's file reference** D/98409 WO
International filing date (day/month/year) 11 October 1999 (11.10.99)	**Priority date** (day/month/year) 16 October 1998 (16.10.98)
Applicant KIRCHHOLTES, Peter, Huub, Gerard, Maria et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 May 2000 (15.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
D/98409 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/07768	11/10/1999	16/10/1998
International Patent Classification (IPC) or national classification and IPC C07J1/00		
Applicant AKZO NOBEL N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/05/2000	13.11.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Friebel, F Telephone No. +49 89 2399 8552

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/07768

I. Basis of th report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-9 as originally filed

Claims, No.:

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (und r Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (som of) the amendments had not b en made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-6,8
	No:	Claims	1-3, 7, 9-14
Inventive step (IS)	Yes:	Claims	4-6,8
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

point V:

What is claimed, is in the first line the compound Tibolone having a high purity; the characterizing feature is the low Δ4 isomer content. This impurity is present in an amount of less than 0.5%, preferably less than 0.25% up to less than 0.1% (see Claims 1 to 3).
In addition to these compound claims there are process claims (Claims 4-6 and 8) and claims relating to pharmaceutical compositions (dosage unit).

As concerns the compound claims refering to high purity Tibolone (here called high purity compositions; see in this connection item VIII of this Written Opinion), the IPEA is of the opinion that this subject-matter is no longer novel (Art.33(2) PCT) since Tibolone purified by routine operations as washing, chromatography and /or recrystallization is already described in the scientific as well as in the patent literature; reference is made to the following documents:

EP-A-389035 (D1); for recrystallization and washing, respectively, see the Examples 1 and 2, the purities obtained therewith are given in detail in Example 3.

EP-A-613687 (D2); this document refers back to D1 and underlines the improved stability, bioavailability and shelf-life of crystalline pure Tibolone, see page 2, the next to last paragraph.

Without going into further detail, reference is also made to the papers of **DECLERCQ (D3)** and **WIELAND (D4)**; in particular DECLERCQ uses Tibolone of high purity for X-ray structural analysis.

The amount of the Δ4 isomer as an impurity is not specifically mentioned in these documents, from the data presented it is however clear that in every case the purity of the Tibolone is so high that any by-products including the Δ4 isomer are below the limits given in Claims 1 to 3.

Also the claims relating to pharmaceutical compositions (except Claim 8) do not meet the novelty requirement of Art.33(2) PCT since D1 and D2 disclose already dosage units, for instance tablets, containing high purity Tibolone; see the respective Examples of D1 and D2.

However, as concerns the subject-matter of the process Claims 4 to 6 and the pharmaceutical composition claim (Claim 8) refering thereto, in none of the documents cited in the Intern.Search Report an aging step for the Tibolone crystals in the presence of water is disclosed or even made obvious; novelty and inventive step are acknowledged (Art.33(2) (3) PCT).

point VIII:

Furthermore, the language of the compound claims 1 to 3 is also open to objection under Art. 6 PCT. These claims refer to a composition containing a certain amount of the Δ4 isomer, however, from the description it becomes evident that not a composition comprising Tibolone but a high purity Tibolone as such is apparently meant. Otherwise the % values would make no sense in that a composition can contain further constituents and the amount of the Δ4 isomer is given relative to the composition and not to the Tibolone. In other words, a composition can comprise for instance the active ingredient Tibolone in an amount of lets say 1% and the Δ4 isomer in an amount of 0.5%, this would be far more than a minor impurity.

The same clarity objection applies to the pharmaceutical composition Claims 9 and 13: what is meant for instance with the definition '*having a shelf life specification comprising less than 5% of Δ4 isomer*'?